PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

INVITATION TO PAY ADDITIONAL FEES

(PCT Article 17(3)(a) and Rule 40.1)

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Date of mailing *(day/month/year)* 27/04/2009

Applicant's or agent's file reference
506612001740

PAYMENT DUE within **ONE MONTH** from the above date of mailing

International application No.
PCT/US2007/023675

International filing date *(day/month/year)* 09/11/2007

Applicant
XDX, INC.

1. This International Searching Authority

(i) considers that there are 2 *(number of)* inventions claimed in the international application covered by the claims indicated ~~below~~/on the extra sheet:

and it considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated ~~below~~/on the extra sheet:

(ii) [X] has carried out a partial international search (see Annex) [ ] will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.:
see annex

(iii) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid

2. The applicant is hereby **invited,** within the time limit indicated above, to pay the amount indicated below:

EUR 1.700,00 x 1 = EUR 1.700
Fee per additional invention — number of additional inventions — total amount of additional fees

Or, _____ x _____ = _____

The applicant is informed that, according to Rule 40.2(c), **the payment of any additional fee may be made under protest,** i.e., a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive.

3. [ ] Claim(s) Nos. _____ have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the International Searching Authority
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Authorized officer
Andrea Pfau

Form PCT/ISA/206 (July 1992)

Invitation to Pay Addl Fee
DOCKETED 8S
5/17/09
5/17/09-E

INVITATION TO PAY ADDITIONAL FEES

International application No.
PCT/US2007/023675

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-6, 13-25, 28-35 complete and 36-38 all partially

   Method of diagnosing or monitoring the status and predicting flare in a patient with systemic lupus erythematosus comprising the detection of gene expression of the genes of table 1 and method for producing a probe set for diagnosing or monitoring SLE by selecting genes of table 1.

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2. claims: 7-12, 26, 27, 39 complete and 36-38 all partially

   Method of diagnosing a patient as having a longitudinally stable classification of SLE comprising detecting the expression of genes of table 2 correlating with expression of IFI27 and method for producing a probe set for diagnosing or monitoring SLE by selecting genes of table 2.

The common concept disclosed in the application is considered as the provision of methods employing expression of genes related to systemic lupus erythematosus (SLE) in a patient.

However, this concept was well known at the date of priority with regard to e. g. D1(XP002516812) disclosing microarray analysis of gene expression in SLE. D1 outlines the methods and results of several studies concerning gene expression analysis by microarray in SLE employing statistical methods for result evaluation and diagnosis of SLE (whole document). It is implicit to D1 that methods for designing probes that were immobilized on the microarrays were employed.
The common concept of association of altered gene expression levels with SLE is also disclosed in D2 (XP008087445) (whole document) and D3 (XP002516813) (whole document). D4 (XP002292183) discloses a method for diagnosing or monitoring the status of systemic lupus erythematosus in a subject by gene expression analysis of blood mononuclear cells on U95AV2 Affymetrix oligonucleotide microarrays containing 12.561 human genes and further gene expression is related to disease activity and classified by SLEDAI (table III, whole document).

In view of this prior art and the fact that expression markers claimed are functionally and structurally unrelated, the above identified single general concept is not novel and can therefore not be the single general inventive concept as required by Rule 13(1) PCT.

The problem to be solved in the present application is thus considered to be the provision of methods employing alternative genes whose expression is related to SLE.

The solutions provided by the present application to the above mentioned problem as defined by the claims is the provision of methods for diagnosing SLE by detecting expression of the genes of table 1 and the provision of methods for classifying a patient as having type I or type

II SLE by correlating gene expression with the expression of IFI27 and genes whose expression correlates with IFI27 as listed in table 2 and five rise to the two inventions as defined above.

Because no other technical features can be distinguished which, in view of the prior art could be regarded as special technical features in the sense of Rule 13(1) EPC, the Examiner is of the opinion that there is no single inventive concept underlying all these solutions.

Should the applicant choose to pay additional fees for one (or more) not yet searched inventions, then the further searches may reveal further prior art that gives evidence of a further lack of unity "a posteriori" within one (ore more) of the not yet searched groups of inventions.

In such a case only the first invention in this (each of these) group(s) of inventions, which is considered to lack unity of invention, will be the subject of a search. Alternatively, the applicant is invited to indicate explicitly, when Paying the Additional Fees, that he wishes a specific embodiment, within a not yet searched invention, to be searched in case a further non-unity is found.

No further invitation to pay further additional fees will be issued. This is because Article 17(3)(a) PCT stipulates that the ISA shall establish the International Search Report on those parts of the international application which relate to the invention first mentioned in the claims ("main invention") and for those parts which relate to inventions in respect of which the additional fees were paid. Neither the PCT nor the PCT guidelines provide a legal basis for further invitations to pay further additional search fees (W17/00, point 11 and W1/97, points 11-16).

The ISA has therefore formulated invention 1 (claims 1-6, 13-25, 28-35 complete and 36-38 all partially) and outlined further groups of inventions according to the solutions provided of which the first invention is subject of the underlying Search Report.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 206

Continuation of Box 4.

Claims Nos.: 1-39 partially

Present claims 1-39 relate to an extremely unlimited number of possible biomarkers and combinations thereof for detection of early stages of infection, SIRS or sepsis. The application does neither disclose nor support the selection of defined, specific expression biomarkers into a diagnostic set. The combination of expression markers to an unlimited number of arbitrary diagnostic sets according to the claims is thus neither disclosed, nor supported or clear. In fact, the claim contains so many options that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Furthermore, not any expression biomarkers and possible combinations thereof are disclosed and supported according to the requirements of Articles 5 and 6 PCT.

Consequently, a search could be carried out for those parts of the application which do appear to be clear and which are disclosed and supported, namely:

1) a method for diagnosing SLE by detecting gene expression of the genes of table 1.

2) a method of classifying a patient having type I or type II SLE by correlating gene expression with the expression of IFI27 and genes whose expression correlates with IFI27 as listed in table 2.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as IPEA is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

Annex to Form PCT/ISA/206
COMMUNICATION RELATING TO THE RESULTS OF THE PARTIAL INTERNATIONAL SEARCH

International Application No
PCT/US2007/023675

1. The present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It shows the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos.:
see 'Invitation to pay additional fees'
2. This communication is not the international search report which will be established according to Article 18 and Rule 43.

3. If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.

4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CROW MARY K ET AL: "Microarray analysis of gene expression in lupus." ARTHRITIS RESEARCH & THERAPY 2003, vol. 5, no. 6, 2003, pages 279-287, XP002516812 ISSN: 1478-6362 the whole document	1-6, 13-25, 28-38
Y	MANDEL M ET AL: "Gene expression studies in systemic lupus erythematosus" LUPUS, BASINGSTOKE, GB, vol. 15, no. 7, 1 July 2006 (2006-07-01), pages 451-456, XP008087445 ISSN: 0961-2033 the whole document	1-6, 13-25, 28-38
Y	CENTOLA M ET AL: "Genome-scale assessment of molecular pathology in systemic autoimmune diseases using microarray technology: a potential breakthrough diagnostic and individualized therapy-design tool." SCANDINAVIAN JOURNAL OF IMMUNOLOGY SEP 2006, vol. 64, no. 3, September 2006 (2006-09), pages 236-242, XP002516813 ISSN: 0300-9475 the whole document	1-6, 13-25, 28-38

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[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BENNETT LYNDA ET AL: "Interferon and granulopoiesis signatures in systemic lupus erythematosus blood" JOURNAL OF EXPERIMENTAL MEDICINE, ROCKEFELLER UNIVERSITY PRESS, JP, vol. 197, no. 6, 17 March 2003 (2003-03-17), pages 711-723, XP002292183 ISSN: 0022-1007 the whole document	1-6, 13-25, 28-38
Y	KIROU KYRIAKOS A ET AL: "Coordinate overexpression of interferon-alpha-induced genes in systemic lupus erythematosus." ARTHRITIS AND RHEUMATISM DEC 2004, vol. 50, no. 12, December 2004 (2004-12), pages 3958-3967, XP002516814 ISSN: 0004-3591 the whole document	1-6, 13-25, 28-38
A	RUS VIOLETA ET AL: "Expression of cytokine- and chemokine-related genes in peripheral blood mononuclear cells from lupus patients by cDNA array." CLINICAL IMMUNOLOGY (ORLANDO, FLA.) MAR 2002, vol. 102, no. 3, March 2002 (2002-03), pages 283-290, XP002516815 ISSN: 1521-6616 the whole document	1-6, 13-25, 28-38